
Reexamining hydroxamate inhibitors of botulinum neurotoxin serotype A: Extending towards the beta-exosite.

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Public Summary:

Botulinum neurotoxins (BoNTs) are the most toxic proteins known to man, exposure to which results in characteristic flaccid paralysis. Given their extreme potency (the lethal dose for a 70 kg person is approximately 70 ng of toxin), these proteins have become studied as possible weapons of bioterrorism; however, effective treatments that function after intoxication have not progressed to the clinic. Here, we have reexamined one of the most effective small molecule inhibitors, 2,4-dichlorocinnamyl hydroxamate, in the context of the known plasticity of the BoNT/A light chain metalloprotease. Our studies have shown that modifications of this compound are tolerated and result in improved inhibitors, with the best compound having an IC₅₀ of 0.23 μ M. Given the inconsistency of structure-activity relationship trends observed across similar compounds, this data argues for caution in extrapolating across structural series.

Scientific Abstract:

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